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Updated Postlicensure Surveillance of the Meningococcal C Conjugate Vaccine in England and Wales: Effectiveness, Validation of Serological Correlates of Protection, and Modeling Predictions of the Duration of Herd Immunity▽

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Meningococcal serogroup C conjugate (MCC) vaccines were licensed in the United Kingdom more than 10 years ago based on correlates of protection that had previously been established for serogroup C-containing polysaccharide vaccines by using the serum bactericidal antibody (SBA) assay. These correlates of protection were subsequently validated against postlicensure estimates of observed vaccine effectiveness up to 7 to 9 months after the administration of the MCC vaccine. Vaccine effectiveness was, however, shown to fall significantly more than 1 year after the administration of a 3-dose course in infancy. Despite this finding, the marked impact on serogroup C disease has been sustained, with the lowest recorded incidence (0.02 case per 100,000 population) in the 2008-2009 epidemiological year, mainly due to the indirect herd immunity effect of the vaccine in reducing carriage. Updated estimates of vaccine effectiveness through 30 June 2009 confirmed high short-term protection after vaccination in infancy, at 97% (95% confidence interval [CI], 91% to 99%), falling to 68% (95% CI, −63% to 90%) more than a year after vaccination. The observed vaccine effectiveness more than 12 months postvaccination was consistent with measured declining SBA levels, but confidence intervals were imprecise; vaccine effectiveness estimates were consistent with SBA titers of 1:4 or 1:8 as correlates of long-term protection after a primary course in infants. Modeling suggested that protection against carriage persists for at least 3 years and predicted the stabilization of serogroup C disease at low levels (fewer than 50 cases per year) up to 2015-2016.

Meningococcal serogroup C conjugate (MCC) vaccines were introduced into the United Kingdom immunization schedule more than 10 years ago, in 1999, as a 2-, 3-, and 4-month primary schedule and as a single-dose catch-up campaign for 1- to 18-year-olds (22). The vaccines were licensed on the basis of safety and immunogenicity studies, and postlicensure surveillance has been crucial in validating serologic correlates of protection, estimating vaccine effectiveness, and interpreting vaccine impact. Serum bactericidal antibody (SBA) was established as a serologic correlate of protection against meningococcal disease in military recruits (14) in the 1960s by using human serum as the exogenous complement source (hSBA).

MCC vaccine trials have shown the vaccines to be safe and immunogenic (4, 10, 17, 22, 26, 27), as measured indirectly through established correlates of protection for serogroup C-containing polysaccharide vaccines. Given the relatively low incidence of serogroup C disease and the logistic difficulties of mounting very large efficacy trials (11), the regulatory authorities indicated that licensure of MCC vaccines would be considered on the basis of immunogenicity and safety data alone (22) by using the SBA correlates of protection established for serogroup C polysaccharide vaccines. There was no standardized commercial source of exogenous human complement, and induction of SBA using rabbit complement (rSBA) in a high percentage of vaccinees was demonstrated as an indicator of protective efficacy (5). It was agreed that licensure of the MCC vaccine in the United Kingdom would be based on the percentage of vaccinees achieving rSBA titers of 8 or greater (22).

Shortly after the introduction of the MCC vaccine, interpretations of rSBA titers as correlates of protection were validated against estimates of observed vaccine effectiveness in those offered the vaccine in infancy, as toddlers, and as preschool children (1). An rSBA cutoff titer of ≥4 or ≥8 at 4 weeks postvaccination was most consistent with the observed short-term efficacy. Estimates of predicted effectiveness for all rSBA cutoffs based on 7- to 9-month postvaccination titers were below the observed effectiveness estimates.

Following MCC vaccine introduction, the incidence of serogroup C disease declined markedly (22). Up to 6 years after MCC immunization, vaccine effectiveness (VE), estimated as the direct protection afforded to vaccinated rather than unvaccinated individuals in the same population, was high, at 83 to 100%, in all individuals who had received MCC vaccines between the ages of 5 months and 18 years in the catch-up campaign (9, 35). Direct protection within a year of routine

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infant immunization was 95% (95% CI, 89 to 99%). However, 1 year or more after a primary course in infancy, estimated vaccine effectiveness had fallen significantly to 7% (95% CI, −3,733 to 85%) (9). Despite this rapid waning of vaccine effectiveness after infant immunization, the population impact on serogroup C disease was maintained because of the striking reduction in serogroup C carriage as a result of the catch-up vaccination program, leading to herd immunity (18, 19, 24). It was assumed that long-term protection would result from the induction of immune memory and the ability to mount a rapid booster response.

Immunogenicity data from studies of a 2-, 3-, and 4-month primary MCC vaccine schedule showed that ≥98% of infants had protective titers after the second dose, and a 2-dose schedule was therefore adequate for priming (10, 26, 29, 31). As a result, it was possible to change the MCC primary vaccine to two doses at 3 and 4 months of age in September 2006, with a booster dose recommended for both the MCC and *Haemophilus influenzae* type b (Hib) conjugate vaccines at 12 months of age by using a combined MCC-Hib conjugate vaccine, irrespective of primary immunization history.

This paper provides a picture of the epidemiology of serogroup C meningococcal disease in England and Wales in the 10 years after the introduction of the MCC vaccine, with updated estimates of vaccine effectiveness through the end of June 2009. Using these data, the main objectives of the paper are (i) to explore the relationship between observed VE and predicted VE based on the percentage of vaccinees with rSBA levels above putative protective thresholds to investigate longer-term correlation and (ii) given the fall in VE with time but the continuing herd immunity impact, to estimate the likely duration of protection against carriage and hence future serogroup C disease incidence. This paper therefore considers the longer-term effects of a national MCC immunization program from an individual and population perspective.

MATERIALS AND METHODS

Epidemiological data. National laboratory surveillance data generated by the Health Protection Agency (HPA) Meningococcal Reference Unit (MRU) were used. The MRU receives isolates and samples from laboratories in England and Wales for species confirmation and phenotypic and genotypic characterization. These methods have been fully described elsewhere (15). Laboratory-confirmed invasive meningococcal disease requires the isolation of the organism from a normally sterile body site (usually cerebrospinal fluid [CSF] or blood) or identification of meningococcal DNA in CSF, serum, plasma, EDTA-coagulated whole blood, or joint fluids by using a real-time TaqMan PCR assay.

Data from the Office of National Statistics (ONS) have been used to generate information on deaths from meningococcal disease. Additional deaths have been identified by linking ONS death registrations with a recorded cause of nonspecific meningitis to HPA MRU laboratory-confirmed reports. Thereby, all ONS-reported deaths which have nonspecific meningitis or meningococcal infection as a contributing factor to or the underlying cause of death can be attributed to invasive meningococcal disease by serogroup when they can be linked to a laboratory-confirmed case.

Vaccine effectiveness calculations. Effectiveness calculations were based on cases of confirmed serogroup C infection that occurred in England between January 2000 and June 2009 in individuals who were eligible for the MCC vaccine and for whom an MCC immunization history was obtained. VE was estimated using the screening method (12) according to time since vaccination (or since age 4 months if unvaccinated). Only children who received full vaccination, defined as the full primary course recommended for their birth cohort (3 doses by their 1st birthday in courses started before 4 September 2006, 2 doses by their 1st birthday thereafter, or a single dose administered after their 1st birthday), or no vaccination were included. Methods have been fully described previously (35), and VE was estimated by use of the following equation: VE = 1 − [PCV(1 − PPV)]/[(1 − PCV)PPV], where PCV is the proportion of the cases of serogroup C disease in individuals who were vaccinated and PPV is the proportion of the population that was vaccinated (i.e., vaccine coverage). Annual national coverage statistics published by the Department of Health were used for coverage by 12 months of age (from April 2001) and by 24 months of age (from April 2002) after introduction of the MCC vaccine (http://www.ic.nhs.uk/statistics-and-data-collections/health-and-lifestyles/immunisation/nhs-immunisation-statistics-england-2007-08-[ns]).

TABLE 1. Distribution of rSBA titers after vaccination with the MCC vaccine by time since completion of the primary schedule[a]

Time since third primary MCC vaccine (mo)	No. of individuals with an rSBA titer of:							Total no. of individuals
	<4	4	8	16	32	64	≥128	
1–11	12	3	5	2	7	13	70	112
12–23	71	1	2	5	12	5	16	112
24–35	32	3	1	6	4	2	4	52
36–56	85	2	5	5	5	5	24	131

[a] The primary vaccination schedule is recommended at 2, 3, and 4 months of age.

In this paper, the General Practice Research Database (GPRD) has been used to better ascertain what proportion of the population eligible for routine immunization had received one or two doses of the MCC vaccine (i.e., are partially vaccinated). In the original calculations (35), based on routine COVER (Cover of Vaccination Evaluated Rapidly) data, partial coverage had been assumed at 2%. GPRD data suggested that a higher proportion of the population was partially vaccinated (about 70% of people not fully vaccinated were partially vaccinated). Thus, the population of truly unvaccinated people was smaller than previously assumed (9). These estimates of partial vaccination were used to update the vaccine effectiveness calculations.

Comparisons of observed effectiveness and predicted vaccine effectiveness based on SBA data. When observed vaccine effectiveness was calculated, cases of serogroup C disease in people who were eligible for routine infant MCC immunization between January 2000 and June 2009 inclusive (this period contains the changeover from a 3-dose to a 2-dose primary schedule) were included. Only those people receiving full vaccination or no vaccination were incorporated. Methods were as described above, but 4 periods of time since vaccination were considered: <12 months, 12 to 23 months, 24 to 35 months, and ≥36 months. Coverage was estimated by using data obtained from the GPRD and was corrected for partial vaccination by removing this proportion from the denominator. For the ≥36-month-postimmunization category, the mean time since vaccination was 56 months (range, 43 to 94 months). This mean time since vaccination was longer than that of those from which the postimmunization SBA data were derived, but all cases were retained to maximize power.

Predicted vaccine effectiveness was calculated using rSBA persistence data from a clinical trial in children who received the MCC vaccine in infancy at 2, 3, and 4 months of age (from 2000 to 2003) and from whom blood samples were taken before and 4 weeks after a Hib booster dose given between 6 months and 4 years of age (30). rSBA titers were measured for these samples as previously described (6, 8). Predicted effectiveness was estimated as simply the proportion of individuals with titers greater than or equal to a given cutoff at various intervals after primary vaccination. This is a simpler method than that used previously (1), because the individuals were vaccinated when there was negligible disease or carriage in the population to give rise to protective antibodies though natural exposure. The distribution of rSBA titers in these children is summarized in Table 1. At the time these children were vaccinated, three MCC vaccines were available which were conjugated using tetanus toxoid (NeisVac-C [Baxter Biosciences]) or mutated diphtheria toxoid CRM_{197} proteins (Meningitec [Wyeth] and Menjugate [Novartis]). It is not possible to differentiate between the three MCC vaccines by antibody persistence or calculated vaccine effectiveness.

Modeling predictions of the duration of herd immunity. To incorporate the role of herd immunity in the duration of protection at a population level, a mathematical model of meningococcal transmission, disease, and vaccination was used to predict the future epidemiology of serogroup C meningococcal disease in England and Wales. This model has been described in detail elsewhere (36, 38). It is an age-structured transmission dynamic model of serogroup C carriage, disease, and vaccination. Serogroup C vaccination was introduced into

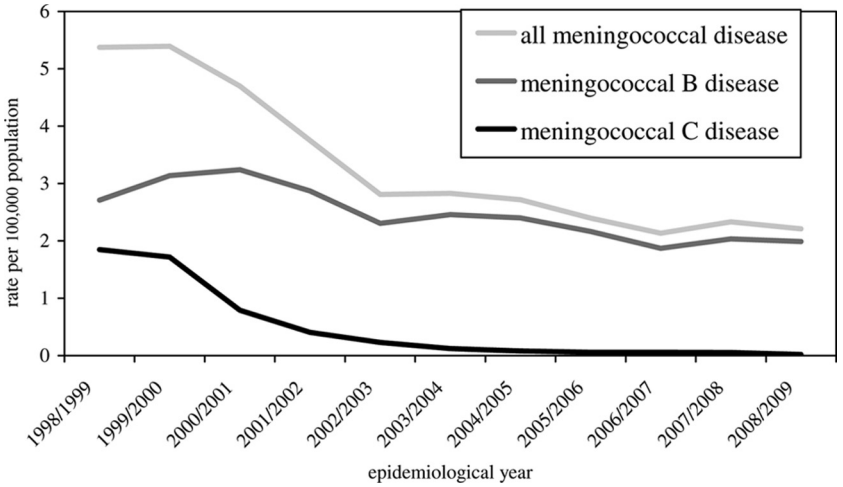

FIG. 1. Incidence of meningococcal disease in England and Wales by epidemiological year between 1998–1999 and 2008–2009.

the model according to the United Kingdom schedule and reported coverage (32). Vaccinated individuals were categorized into routinely immunized and catch-up cohorts and, after vaccination, were protected against acquisition of both serogroup C carriage and disease. Updated vaccine effectiveness estimates through the end of December 2008 were used to parameterize the model.

The model has been further updated to incorporate the changes to the immunization schedule from September 2006, when the primary MCC schedule was changed to 3, 4, and 12 months of age. In the absence of data on the effectiveness of the new schedule, we assumed that vaccine effectiveness is 96% in the short term, but we varied the average duration of protection after receipt of the last dose from 15 months (the same as assumed for the 2-, 3-, and 4-month schedule) to 10 years (as assumed for the catch-up campaign). Two alternative model structures were investigated, as described elsewhere (37). The first model assumes that vaccinated individuals are protected against both carriage and disease for the same time duration, and the second assumes that protection against carriage wanes more rapidly than protection against disease. This implicitly assumes that rSBA titers wane over time and that there is a higher threshold for protection against acquisition of carriage than protection against disease.

RESULTS

Epidemiological data. The epidemiology of meningococcal disease in England and Wales has changed markedly since the introduction of the MCC vaccine in November 1999. The incidence of meningococcal disease due to all serogroups fell from an incidence of 5.37 to 2.21 per 100,000 population between the 1998-1999 and 2008-2009 epidemiological years (Fig. 1). The marked reduction in serogroup C disease has had a major impact on the observed change, but the fall has also, in part, been due to a concurrent period of relatively low serogroup B disease in 2001-2002.

In 1998-1999, before the MCC vaccine was introduced, there were 955 confirmed cases and 118 deaths due to serogroup C disease. In 2008-2009, there were only 13 confirmed cases and 2 deaths. The overall incidence of serogroup C disease in England and Wales fell from 1.85 per 100,000 population in 1998-1999 to 0.02 per 100,000 population in 2008-2009 (Fig. 1), a reduction of 98.7%. In the under-20-year age group, the incidence of serogroup C disease fell by 99.1%, from 5.34 to 0.03 per 100,000 population, in the same period. There were 78 recorded deaths from meningococcal C disease in England and Wales in those under 20 years of age in 1998-1999. From 1 July 2006 to 30 June 2009, there was one reported death in this age group. Between 1998-1999 and 2007-2008, the incidence of meningococcal C disease in infants under 1 year of age had fallen by 99%, from 16.63 to 0.15 per 100,000 population (Table 2). There were no confirmed cases in this age group in 2008-2009, and the last ONS-recorded deaths were in 2002-2003 (as of December 2009).

The use of the MCC vaccine was extended in January 2002 so that it could be offered to all individuals up to 25 years of age. Reductions in disease were also seen in those aged 25 years and over, the vast majority of whom would not have been offered the MCC vaccine. Incidence of serogroup C disease in this age group fell from 0.55/100,000 population to 0.02/

TABLE 2. Incidence of meningococcal serogroup C disease in England and Wales by epidemiological year

Age (yr)	No. of cases (per 100,000)										
	1998-1999	1999-2000	2000-2001	2001-2002	2002-2003	2003-2004	2004-2005	2005-2006	2006-2007	2007-2008	2008-2009
<1	16.63	10.56	3.30	1.02	1.02	0.33	0.16	0.16	0.31	0.15	0.00
1–4	8.13	8.96	1.77	0.92	0.53	0.46	0.17	0.12	0.12	0.08	0.04
5–9	2.60	3.23	0.80	0.15	0.15	0.03	0.03	0.03	0.06	0.03	0.03
10–14	2.68	2.35	0.32	0.17	0.00	0.03	0.03	0.03	0.00	0.00	0.06
15–19	6.54	3.74	1.19	0.53	0.27	0.03	0.09	0.06	0.03	0.11	0.00
20–24	1.44	1.71	2.14	0.98	0.53	0.21	0.09	0.09	0.06	0.05	0.00
≥25	0.55	0.66	0.57	0.34	0.20	0.11	0.08	0.05	0.05	0.05	0.02
All ages	1.85	1.72	0.79	0.40	0.23	0.12	0.08	0.06	0.06	0.05	0.02

100,000 population between 1998-1999 and 2008-2009, a reduction of 95.6%. Similarly, in infants under 3 months of age, who could not have received a complete primary course of the MCC vaccine, there were 11 cases in 1998-1999 and only 1 case since 2006-2007. These findings are consistent with a herd immunity effect.

Vaccine effectiveness. Vaccination histories were ascertained for 594 (99.7%) of the 596 confirmed serogroup C cases in England and Wales from 1 January 2000 to 30 June 2009 in individuals born on or after 9 January 1981 and therefore targeted by the MCC catch-up campaign or for ongoing routine vaccination. Seventy-seven of the 594 cases were not eligible for the MCC vaccine at the time of their illness (i.e., the vaccine had not yet been made available to their school year group or they had only recently entered the country), 415 eligible children had not received any doses of vaccine prior to their disease onset, and for one child the date of vaccination was not known. One hundred two children had received one or more doses of the MCC vaccine before disease onset. Of these 102 children, 77 were categorized as true vaccine failures, 72 of which were living in England and were therefore included in the calculations of vaccine effectiveness.

The remaining 25 cases who had received the MCC vaccine before disease onset did not fit the case definition of a true vaccine failure; 20 had not completed their primary course, and in 5 cases, disease occurred too soon (less than 10 days) after vaccination. A true MCC vaccine failure is defined as confirmed invasive meningococcal serogroup C disease with onset at least 10 days after the last dose of a completed primary course (as appropriate for that individual's birth cohort) of the MCC vaccine in that individual (2). No booster doses of the MCC-Hib vaccine had been administered prior to disease onset in the confirmed cases in the time period identified, and effectiveness of the booster dose was therefore not considered.

Based on available data through the end of June 2009, VE within 12 months of routine infant immunization was estimated at 97% (95% CI, 91% to 99%). At 12 months or more after routine immunization, effectiveness was estimated at 68% (95% CI, −63% to 90%). The difference in effectiveness between less than 1 year and 1 year or more after routine immunization was statistically significant ($P < 0.01$).

Estimates of effectiveness in all other age cohorts ranged between 83 and 97%, with no significant fall in effectiveness in each age cohort between time periods less than a year and 1 year or more since immunization (Table 3). Previously, a significant but small fall in effectiveness was found when age cohorts from 3 to 18 years were combined (35). With these latest data, there was no significant decline in overall effectiveness in the 3- to 18-year age groups 1 year or more after immunization ($P = 0.13$). Vaccine effectiveness in toddlers aged 1 to 2 years who had received a single dose of the MCC vaccine was 89% (95% CI, 64% to 98%) up to 1 year after MCC vaccination and 71% (95% CI, −40% to 93%) more than 1 year after vaccination ($P = 0.23$).

Vaccine effectiveness predicted by different rSBA cutoffs at increasing time intervals after a primary course in infancy. The observed VE after routine immunization decreased gradually with increasing time since completion of a primary course. Observed effectiveness estimates fell from 95.9% (95% CI, 86.6 to 98.8%) within 12 months to 30.7% (95% CI, −2,846

TABLE 3. Calculated meningococcal C conjugate VE in immunized cohorts through June 2009 (England only)

Cohort	Age at time of MCC vaccination	No. of doses scheduled	Observation period, by quarter year	No. of cases of confirmed disease (no. of cases in vaccinated children)[c]			% vaccine effectiveness (95% CI)[b,c]			Difference between results for ≤1 yr and >1 yr since MCC vaccination
				Total	Within 1 yr of vaccination	>1 yr after vaccination	Overall	Within 1 yr of vaccination	>1 yr after vaccination	
Routine[a]	2, 3, and 4 mo	2 or 3	Q1 2000–Q2 2009	48 (37)	14 (6)	34 (31)	90 (77–95)	97 (91–99)	68 (−63–90)	$P < 0.01$
Infant catch-up	5–11 mo	2	Q3 2000–Q2 2009	14 (5)	4 (1)	10 (4)	86 (54–96)	91 (−8–100)	84 (31–97)	$P = 0.63$
Toddler catch-up	1–2 yr	1	Q3 2000–Q2 2009	25 (10)	15 (4)	10 (6)	83 (60–93)	89 (64–98)	71 (−40–93)	$P = 0.23$
Preschool catch-up	3–4 yr	1	Q3 2000–Q2 2009	40 (3)			97 (90–99)			
Infant school catch-up	4–6 yr	1	Q3 2000–Q2 2009	17 (1)			93 (56–100)			
Junior school catch-up	7–10 yr	1	Q3 2000–Q2 2009	10 (3)	91 (6)[d]	77 (14)[d]	93 (72–99)	96 (92–99)[d]	93 (87–96)[d]	$P = 0.13$[d]
Secondary school catch-up	11–16 yr	1	Q2 2000–Q2 2009	52 (8)			97 (93–99)			
Sixth-form catch-up	17–18 yr	1	Q1 2000–Q2 2009	49 (5)			92 (81–98)			
Total				255 (72)	124 (17)	131 (55)				

[a] Using GPRD data (see the text). The routine cohort includes individuals who would have been offered 2 or 3 doses as a primary course when they were less than 1 year of age according to the recommended schedule at that time. Only one child, who was unvaccinated, falls into the 2-dose cohort.

[b] Vaccine effectiveness compares children eligible for complete vaccination who had received all scheduled doses versus children who received no doses. Partially vaccinated children were excluded.

[c] Unvaccinated cases are based on the date-of-birth cohort each individual belongs to.

[d] Preschool to sixth-form cohorts (ages 3 to 18 years) combined.

TABLE 4. Estimation of VE by time since vaccination for the routine cohort

Time since vaccination (mo)	No. of vaccinated children	No. of unvaccinated children	% of children vaccinated	% of population vaccinated	% VE (95% CI)
<12	6	8	43	95	96 (87–99)
12–23	10	1	91	97	68 (−1,300–95)
24–35	8	1	89	95	60 (−1,700–95)
≥36	13	1	93	95	31 (−2,800–90)

to 89.6%) 36 months or more after the third dose of the MCC vaccine (Table 4). The effectiveness predicted on the basis of the proportions of vaccinated individuals with rSBA titers at or above 4, 8, and 128 at different time intervals are shown in Table 5. These estimates were compared with the observed effectiveness at different time intervals since vaccination and are summarized in Fig. 2, 3, and 4.

The observed effectiveness was higher than the estimated effectiveness at most time intervals for each cutoff titer, but cutoffs of 1:8 and 1:4 provided similar results which were consistent with observed effectiveness. The closest fit using a 1:4 or a 1:8 cutoff was for VE within a year of immunization, for which tight confidence intervals were calculated due to the larger number of unvaccinated cases. VE was estimated with low precision for the period >1 year postvaccination, so validation of the correlate of protection in this period is difficult. The predicted VE using the 1:128 cutoff is clearly different from the observed VE seen within 12 months. This suggests that 1:128 is not an appropriate cutoff, in line with previous findings (1).

Modeling predictions of the duration of protection against carriage. The numbers of cases of serogroup C disease predicted by modeling three different scenarios are shown in Fig. 5. The scenario that is most consistent with the observed data sits between the model that assumes 3 years of protection against carriage in the catch-up cohorts and the model assuming 10 years of protection against carriage. The 3-year protection model predicts stabilization of disease levels at between 30 and 40 cases each year until 2015-2016, while, less realistically, the 10-year protection model predicts that the disease will die out. The model assuming that vaccinees derive only 1 year of protection against carriage predicts substantially more cases than what has been observed.

TABLE 5. Predicted VE by time since vaccination for the routine cohort based on an assumption of protection with rSBA titers of ≥1:4, ≥1:8, and ≥1:128

Titer cutoff and time since vaccination (mo)	No. of immunized individuals with:		% VE (95% CI)
	Protective titers	Unprotective titers	
≥1:4 cutoff			
<12	100	12	89 (82–94)
12–23	41	71	37 (28–46)
24–35	20	32	39 (25–53)
≥36	46	85	35 (27–44)
≥1:8 cutoff			
<12	97	15	87 (79–92)
12–23	40	72	36 (27–45)
24–35	17	35	33 (20–47)
≥36	44	87	34 (26–42)
≥1:128 cutoff			
<12	70	42	63 (53–72)
12–23	16	96	14 (8–22)
24–35	4	48	8 (2–19)
≥36	24	107	18 (12–26)

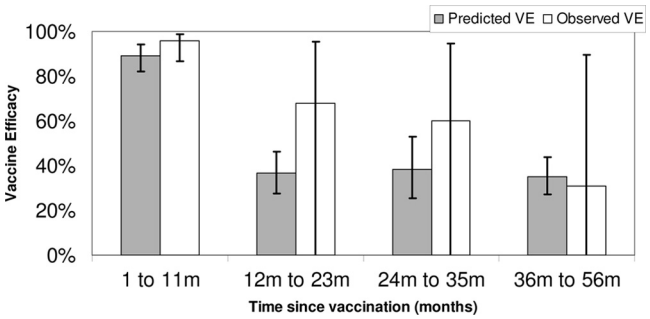

FIG. 2. Predicted MCC vaccine effectiveness (VE) and observed MCC vaccine effectiveness, using a 1:4 cutoff, by months (m) since vaccination, with a 95% CI.

The model incorporated the changes to the routine immunization schedule that were introduced in 2006. Using the first model scenario (assuming 3 years of protection), we varied our assumptions about the duration of protection following this schedule from an average of 15 months of protection up to an average of 10 years of protection following the receipt of the last dose to represent the likely extremes based on observations in other age groups. The numbers of cases predicted by the model were fairly insensitive to these assumptions, with fewer than 10 additional cases predicted to occur each year in the group with the shortest duration of protection than in the group with the longest duration of protection. This is because the herd effects resulting from the catch-up campaign persist, and this effect is dominant in determining the number of cases.

DISCUSSION

When the MCC vaccine was introduced in the United Kingdom, a comprehensive national surveillance system was established concurrently. This was essential to provide epidemiologic and laboratory data to assess and continue to inform the

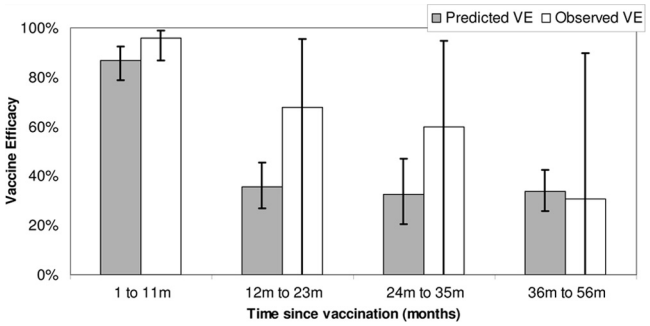

FIG. 3. Predicted MCC vaccine effectiveness (VE) and observed MCC vaccine effectiveness, using a 1:8 cutoff, by months (m) since vaccination, with a 95% CI.

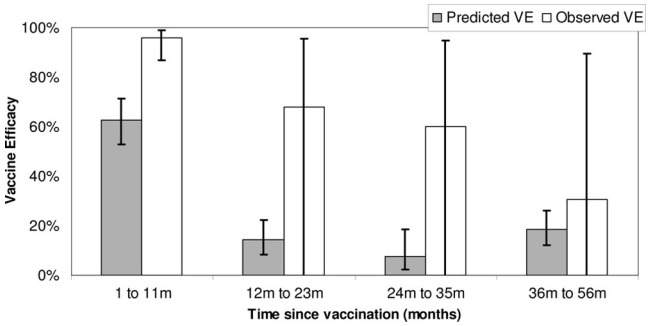

FIG. 4. Predicted MCC vaccine effectiveness (VE) and observed MCC vaccine effectiveness, using a 1:128 cutoff, by months (m) since vaccination, with a 95% CI.

MCC vaccine program. Early surveillance data demonstrated a marked and rapid reduction in serogroup C disease in close temporal association with the introduction of the vaccine into each identified age cohort (22) and an associated fall in deaths. The most recent epidemiologic data have shown further reductions in serogroup C disease and fewer deaths in the population offered vaccination. In those under 20 years of age, the incidence of serogroup C disease fell from 5.34 to 0.03 per 100,000 population between 1998-1999 and 2008-2009, a reduction of 99.4%. There has been one death recorded in this age group over the last 3 epidemiologic years. Observed effectiveness, based on nearly 10 years of experience with the MCC vaccine, was consistent with this marked direct impact. Overall effectiveness was estimated to be between 83 and 97% in each targeted age cohort. However, in line with earlier data (35), calculated effectiveness 1 year or more after primary infant immunization declined significantly from 97% to 68%, with evidence of a gradual decline over time (Table 4). While estimates of observed effectiveness a year or more after vaccination fell in all other age cohorts, in comparison to effectiveness less than a year after immunization, this decrease did not reach significance.

MCC vaccines are T-cell-dependent antigens shown to induce a booster response up to 4 years after completion of infant immunization via immune memory (7). It was postulated that they would provide long-term protection as a result of rapid boosting of SBA levels on exposure and that this effect would endure even without a booster. This assumption was based on the United Kingdom's experience with Hib conjugate vaccines (given at 2, 3, and 4 months of age), which were thought to be providing long-term protection via immune memory despite waning Hib antibody levels (13). The original Hib vaccine effectiveness estimates did not tease out the relative contributions of direct and indirect protection; direct protection from the Hib conjugate vaccine given in the first year of life was subsequently shown to be short-lived (23, 25). The presence of immune memory (as currently measured by avidity maturation and booster response) may not always be predictive of long-term protection, as both MCC and Hib conjugate vaccine failures have been shown to occur in children who have been primed and in whom immune memory can be demonstrated (2, 21). This confirms that the ability to generate an immune memory response to the serogroup C capsular polysaccharide does not necessarily confer long-term protection.

Seroprevalence studies of infants and adolescents have shown that the decline in effectiveness in infants paralleled the decline in SBA, while SBA titers in adolescents showed little evidence of a decline with time, mirroring the sustained high effectiveness in this age group (27, 39). Our SBA data similarly indicate a fairly rapid fall in the proportion of children with SBA titers of ≥ 8 within the first 12 months after primary immunization, followed by relative stability (Table 1). From the available data, it is not possible to ascertain whether the higher SBA levels after 12 months were in individuals who

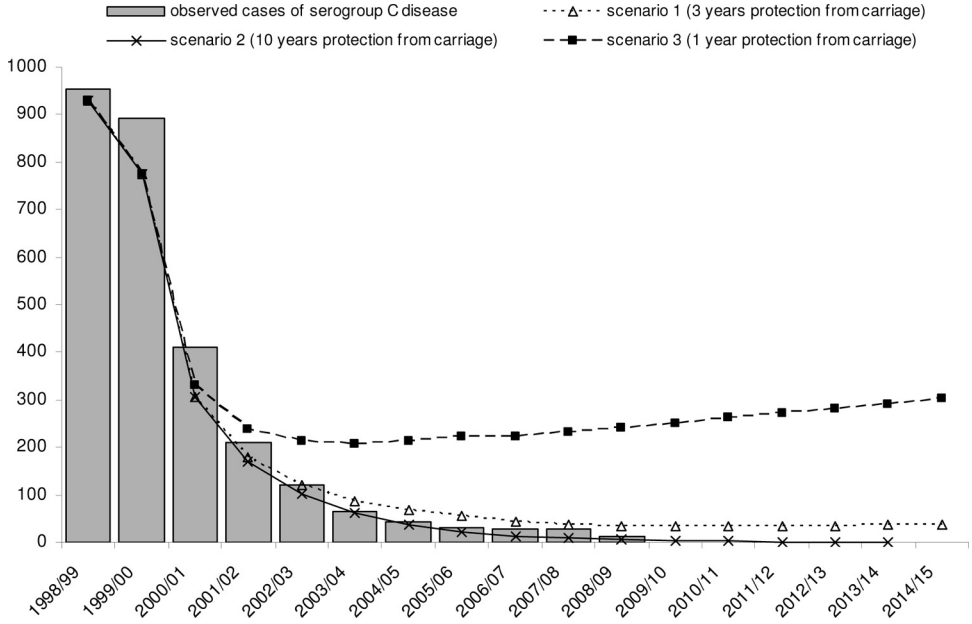

FIG. 5. Model predictions and observed cases of laboratory-confirmed serogroup C disease in England and Wales.

sustained higher SBA levels or if levels generally fell below detection and the raised SBAs were a consequence of boosting from circulating serogroup C organisms in exposed individuals at that time. However, exposure to serogroup C organisms is now unlikely. Even between 1996 and 1999, before the MCC vaccine was introduced and when circulation of serogroup C organisms would be expected, 87.3% of 1-year-olds had rSBA titers of <8 (34).

In order to establish a population-based correlate of protection, we used rSBA titers at different cutoff levels in vaccinated and unvaccinated populations to estimate VE. The cutoff at 1:128 was, as previously shown, inconsistent with observed effectiveness. An rSBA 1:4 or 1:8 cutoff was consistent with observed effectiveness, although predicted VE for each of these would be lower than that observed. The methods used to obtain the observed and predicted VE estimates should not be affected by the large herd immunity effect seen for meningococcal group C. This is because it was assumed that there was no circulating serogroup C when predicting VE and because it is assumed that herd immunity has the same effect on both the vaccinated and unvaccinated population when estimating VE.

Observed VE more than 12 months postvaccination was consistent with the declining antibody levels, but the confidence intervals were imprecise, and at this point we cannot validate rSBA titers of 1:4 or 1:8 as correlates of long-term protection after a primary course in infants. Long-term efficacy would seem to depend on circulating SBA levels at the time of exposure rather than the ability to boost. The booster dose of the MCC vaccine (in the form of an MCC-Hib combination vaccine) was introduced in September 2006, with the expectation that elevated rSBA titers would then persist throughout adolescence. However, the kinetics of antibody persistence following boosting in the second year of life was shown to be similar to that following the primary MCC vaccination schedule (8). Two years following boosting, the percentage of subjects with rSBA titers of ≥8 was between 22% and 43%, depending on the priming MCC vaccine used, giving an indication that additional booster doses of the MCC vaccine may be required in the future to maintain protective antibody levels.

The United Kingdom's experience with Hib vaccine established the importance of a reduction in carriage (3, 16, 20) and induction of herd immunity in the long-term control of disease. MCC immunization has been shown to significantly reduce nasopharyngeal carriage of serogroup C meningococci (18) for at least 2 years with no evidence of serogroup replacement (19). Early evidence of a herd immunity effect in unimmunized individuals who were eligible for the MCC vaccine (24) was shown by comparison of the serogroup C attack rates in age groups targeted by the MCC campaign in one complete epidemiologic year before and after the introduction of the MCC vaccine, which demonstrated an overall reduction of 67%.

Protection against carriage, and the resultant herd immunity effect induced by the MCC catch-up campaign, is considered the major determinant of the program's outcome and cost-effectiveness (33). However, the duration of herd immunity is not known, and the mechanisms for conferring herd immunity are currently poorly understood. One of the key factors to consider is the duration of protection against carriage conferred on vaccinees. Unfortunately, there are no established correlates of protection for serogroup C carriage so this cannot be measured in seroepidemiology studies. The model scenario that appears to be most consistent with the observed number of serogroup C cases suggests that the indirect effects of the catch-up campaign are likely to persist for several more years. A different waning rate has been applied within the model to individuals immunized routinely and those immunized within catch-up cohorts, and this is consistent with the effectiveness data. However, among individuals who received the MCC vaccine when they were 1 year of age or older, it has been shown that SBA titers decline more rapidly in those who were immunized at a younger age (28). The current model did not take this into account, and while it is anticipated that this would make only a minor overall difference due to the overwhelming effect of the initial catch-up component of the campaign, this is a possible consideration for further refinement of the model.

Should transmission of persisting serogroup C meningococci increase, it is predicted to occur slowly, because transmissibility is low. However, vaccination can prevent carriage of strains only that are expressing a serogroup C capsule; capsule-specific antibodies will not prevent carriage of meningococci that are genotypically group C if the capsule is not expressed. In carriage studies, 81% of clonal complex ST11 strains (the most common cause of serogroup C disease prior to vaccination) that had the group C *siaD* gene expressed a capsule, compared to only 50% of group C strains that were genetically positive for clonal complex ST8 (19), which suggests that herd effects may be greater in populations where ST11 dominates. The models used here do not take into account possible introductions of serogroup C strains that are more transmissible or less likely to express a capsule in the carrier state. These events cannot be predicted and underline the importance of continued high-quality disease surveillance, complemented by seroprevalence studies of serogroup C SBA to identify groups that may be susceptible to infection should transmission increase.

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